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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

JOHANNSSEN, DIANA B

ART UNIT PAPER NUMBER

1634

DATE MAILED: 04/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

Office Action Summary**Application No.**

09/955,367

Applicant(s)

ATTIE ET AL.

Examiner

Diana B. Johannsen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 February 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) 4, 7, 9 and 10 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5, 6, 8 and 11 is/are rejected.
- 7) ☒ Claim(s) 11 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of ADD1/SREBP in the Response of April 11, 2003, is acknowledged. The traversal is on the ground(s) that "any reasonable set" of Applicant's genes "associated with diabetes" could be used in diabetes diagnosis. The response notes that claims 4 and 6 recite a requirement for at least 4 genes, and states that "It is believed that the applicants are entitled to claims of this breadth since the gene expression pattern has been demonstrated to be characteristic of diabetes".
2. In response, it is first noted that subsequent to the Response of April 11, 2003, the examiner revised the restriction requirement to further allow election of a single combination of 4 genes. With regard to applicant's argument that any and all genes encompassed by the genes should be examined because expression of all the recited genes is associated with diabetes, this is not found persuasive. First, many of the genes encompassed by the claims, including those elected by applicants, are shown to be associated with obesity (see Tables 1-2), but not with diabetes or hyperglycemia. Thus, the genes encompassed by the claims are not linked in the manner suggested by Applicants. Further, it is again noted that as each gene and combination of genes encompassed by the claims differs structurally and functionally from every other gene and combination, each gene and combination requires a separate search involving different search terms. Accordingly, as it would pose a serious burden on the examiner to conduct such a multitude of different searches, the requirement is still deemed proper and is therefore made FINAL.

3. Applicant's election of the combination of SREBP, a gene "aa667872" described as "similar to ubiquinol-cytochrome c reductase core protein 2," cytochrome c oxidase subunit VIIIa, and stearyl-CoA desaturase in the Response of February 4, 2004 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

4. Claims 4, 7, and 9-10, and genes and combinations other than those elected as recited above, are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the Response of April 11, 2003.

Specification

5. The use of the trademarks GENBANK, SUPERSSCRIPT, BIOARRAY, RNEASY, and GENEARRAY has been noted in this application. The trademarks should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Claim Objections

6. Claim 11 is objected to because of the following informalities: the term "diabetic" is misspelled "diabetec." Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-3, 5-6, 8 and 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing obesity in a mouse comprising determining decreased expression in adipose tissue of SREBP, alone or in combination with a gene "aa667872" described as "similar to ubiquinol-cytochrome c reductase core protein 2," cytochrome c oxidase subunit VIIIa, and stearyl-CoA desaturase, does not reasonably provide enablement for methods of diagnosing obesity in individuals other than mice, methods of determining a prognosis for obesity, or a diagnosis or prognosis for incipient obesity of the "transition from obese" to diabetes, or for methods of diagnosing diabetes or susceptibility for diabetes. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the

existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

The elected invention is drawn to methods of diagnosing diabetes comprising determining "the expression pattern in the adipose tissue" of SREBP or the combination of SREBP, a gene "aa667872" described as "similar to ubiquinol-cytochrome c reductase core protein 2," cytochrome c oxidase subunit VIIIa, and stearyl-CoA desaturase (claims 1-3 and 5-6), to methods for diagnosing diabetes susceptibility comprising "assaying the expression level of the gene SREBP in the adipose tissue" (claim 8), and to methods "for the diagnosis or prognosis of obesity, incipient obesity, or the transition from obese" to diabetic comprising determining "the expression pattern in the adipose tissue" of SREBP or the combination of SREBP, a gene "aa667872" described as "similar to ubiquinol-cytochrome c reductase core protein 2," cytochrome c oxidase subunit VIIIa, and stearyl-CoA desaturase. The specification teaches that SREBP, a gene "aa667872" described as "similar to ubiquinol-cytochrome c reductase core protein 2," cytochrome c oxidase subunit VIIIa, and stearyl-CoA desaturase each exhibit decreased expression in obese mice (see Table 1 and the description thereof on page 4).

It is unpredictable as to whether one of skill in the relevant art could use applicant's invention in a manner reasonably commensurate with the instant claims. Because Applicant's disclosure provides evidence that SREBP, a gene "aa667872" described as "similar to ubiquinol-cytochrome c reductase core protein 2," cytochrome c

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oxidase subunit VIIIa, and stearyl-CoA desaturase each exhibit decreased expression in adipose tissue of obese mice, one of skill in the art would reasonably consider decreased expression of SREBP, alone or in combination with these other 3 genes, in adipose tissue as one factor in diagnosing obesity in mice. However, the specification does not include these genes among those disclosed in Table 3 as being associated with hyperglycemia and diabetic disease. It is further noted that the specification itself teaches that "only 10% of individuals who are obese are diabetic" (p. 2); accordingly, the teachings of the specification indicate that a gene exhibiting modified expression in an obese individual might or might not exhibit a similar pattern of expression in a diabetic. Further, the specification does not provide evidence that determining the expression of any of these 4 genes would allow one to determine a diagnosis for diabetes susceptibility, prognosis for obesity, diagnosis or prognosis for incipient obesity, or "transition from obese" to diabetic in any type of individual, or a diagnosis of obesity in any individuals other than mice. Thus, the teachings of the specification alone are insufficient to enable the use of the claimed invention, with the exception of obesity diagnosis in mice. Lacking guidance from the specification, one of skill in the art may look to the teachings of the art for further guidance and enablement of a claimed invention. However, in the instant case, the prior art is silent with respect to an association between expression levels of SREBP, alone or in combination with a gene "aa667872" described as "similar to ubiquinol-cytochrome c reductase core protein 2," cytochrome c oxidase subunit VIIIa, and stearyl-CoA desaturase, and diabetes or diabetes susceptibility, as well as obesity and the transition from obesity to diabetes.

Given the high level of skill of one skilled in the relevant art, it is clearly within the ability of such an artisan to carry out further experimentation aimed at identifying such associations. However, the outcome of such further research cannot be predicted, and thus it is unknown as to whether any quantity of experimentation would be sufficient to enable the claimed invention. Thus, it would require undue experimentation to use applicant's invention in a manner reasonably commensurate with the instant claims.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-3, 5-6, 8 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 6 and 11 are indefinite over the recitation of Tables 1 and 2 (in claims 1-3, 6, and 11) and Table 3 (claims 1-3 and 11) in the claims. It is noted that these Tables recite a variety of information, including gene descriptions, as well as mouse gene accession nos. and human homologue accession nos. It is unclear as to what information or subset of information about a particular gene would need to be detected or determined in order to meet the requirements of the instant claims. For example, do the claims encompass any stearoyl-CoA desaturase, or only the particular molecules identified by accession no. in the Tables? The claims are further indefinite because database accession nos. are updated periodically, and therefore do not provide a clear and definite structural description of the molecules encompassed by the claims. Finally, with regard to the molecule "aa667872 described as similar to ubiquinol-cytochrome c

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reductase core protein 2," it is unclear how one could identify such a molecule (which is not provided with a precise structural or functional description, or described by a well-known gene name) without detecting a particular sequence that corresponded to one of the recited accession numbers at the time the invention was made. Clarification is required.

Claims 1-2 are indefinite over the recitation of the language "determining the expression pattern....to determine if the individual has diabetic disease." This language does not apprise one of skill in the art as to how determining an expression pattern actually allows one to determine if the individual has diabetic disease, and how the practice of this step allows one to diagnose diabetes, as required by the preamble of claim 1. Clarification is required.

Claim 2 is indefinite over the recitation of the limitation "the gene" because there is insufficient antecedent basis for this limitation in the claims.

Claim 3 is indefinite over the recitation of the language "determining the expression pattern in the adipose tissue of the individual of a subset of the genes....that subset being determinative of diabetic disease." This language does not apprise one of skill in the art as to how a subset would be "determinative," and as to how the practice of this step allows one to diagnose diabetes, as required by the preamble of the claim. Clarification is required.

Claims 5 is indefinite over the recitation of the language "determining the expression pattern....to determine if the individual has diabetic disease or a genetic predisposition to diabetic disease." This language does not apprise one of skill in the

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art as to how determining an expression pattern actually allows one to determine if the individual has diabetic disease or predisposition thereto, and how the practice of this step allows one to diagnose diabetes, as required by the preamble of the claim.

Further, it is not clear whether the claim is drawn to a method of diagnosing diabetes, or to a method of diagnosing either diabetic disease or a genetic predisposition thereto.

Clarification is required.

Claim 6 is indefinite over the recitation of the language "determining the expression pattern in the adipose tissue of the individual of at least four of the genes....those genes being determinative as to whether the individual has diabetic disease." This language does not apprise one of skill in the art as to how the "at least four" genes would be "determinative," and as to how the practice of this step allows one to diagnose diabetes, as required by the preamble of the claim. Clarification is required.

Claim 8 is indefinite because the claim does not indicate how the step of "assaying the expression level of the gene SREBP in the adipose tissue" of an individual allows one to diagnose susceptibility to diabetes, as required by the claim preamble. Clarification is required.

Claim 11 is indefinite over the recitation of the language "determining the expression pattern in the adipose tissue of the individual of any of the genes....to determine if the individual has gene expression consistent with said diagnosis or prognosis" This language does not apprise one of skill in the art as to what gene expression would be considered to be "consistent" with any of the diagnoses or prognoses recited in the preamble of the claim, and therefore it is unclear as to how the

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performance of this method step would allow one to determine a diagnosis or prognosis for obesity, incipient obesity, or a transition from obesity to diabetes. Clarification is required.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Andreelli et al (Diabetologia 42:358-365 [3/1999]).

It is noted that while the elected invention is drawn to either ADD1/SREBP or to the combination of ADD1/SREBP, a gene "similar to ubiquinol-cytochrome c reductase core protein 2," cytochrome c oxidase subunit VIIIa, and stearyl-CoA desaturase, the instant claim as written is sufficiently broad so as to encompass any gene.

Andreelli et al disclose that insulin induces PI-3K mRNA expression in the adipose tissue of lean and obese (non-diabetic) subjects at a much higher level than in type II diabetics (see entire reference, particularly page 361, right column). In view of Andreelli et al's own teachings, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Andreelli et al so as to assay for PI-3K gene expression levels in the adipose tissue of individuals being screening for type II diabetes following insulin infusion, and to have considered low levels of PI-3K expression (similar to those seen in type II diabetics as compared to individuals who are lean or obese but non-diabetic) as a factor in reaching a diagnosis of diabetes or predisposition to diabetes. As Andreelli et al disclose that a particular pattern of PI-3K expression in adipose tissue following insulin infusion characterizes type II diabetics as compared to lean and obese (non-diabetic) individuals, an ordinary artisan would have been motivated to have made such a modification for the advantage of more accurately diagnosing diabetes or diabetes predisposition.

Conclusion

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 571/272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

A handwritten signature in black ink, appearing to read "Diana B. Johannsen", with a long horizontal flourish extending to the right.

Diana B. Johannsen
Patent Examiner
April 5, 2004